Loncastuximab tesirine (Zynlonta®) as monotherapy for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL)

General information [1]

Drug description	Indication
The active substance of Zynlonta® is loncastuximab tesirine, a monoclonal antibody and drug conjugate. Zynlonta® delivers SG3199, a pyrrolobenzodiazepine dimer cytotoxin, to B-cell malignancies by targeting CD19. Upon binding to CD19, Zynlonta® is internalised and SG3199 is released, resulting in the formation of highly cytotoxic DNA interstrand cross-links, which cause cell-death.	Loncastuximab tesirine (Zynlonta®) as monotherapy is indicated for the treatment of adult patients with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy.

Current treatment [2]

- The most commonly used salvage treatment regimens for relapsed or refractory DLBCL include:
  - R-GDP – rituximab with gemcitabine, dexamethasone and cisplatin
  - R-DHAP – rituximab with dexamethasone, high-dose cytarabine and cisplatin
  - R-ICE – rituximab with ifosfamide, carboplatin and etoposide.
- For adults whose DLBCL is relapsed or refractory after 2 or more systemic therapies NICE recommends:
  - Tisagenlecleucel
  - Axicabtagene ciloleucel.

Regulatory status

EMA [1]	FDA [3]
Approval status for this indication: On 15 September 2022, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Zynlonta®. **UPDATE**: Date of issue of marketing authorisation valid throughout the European Union: 20/12/2022 The full indication is: ❖ Zynlonta® as monotherapy is indicated for the treatment of adult patients with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy. **Other indications**: none ✓ **Medicine received a conditional marketing authorisation[1]** ✓ **Medicine is under additional monitoring**	**Approval status for this indication**: On 23 April 2021, the FDA granted accelerated approval to loncastuximab tesirine-lpyl (Zynlonta™) for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low grade lymphoma, and HGBL. ✓ Accelerated approval based on overall response rate ✓ Priority review ✓ Orphan drug designation **Other indications**: none

Costs

1 vial Zynlonta® powder for solution for infusion 10 mg = 15,750.00 (ex-factory price) [4]

Premedication [5]

❖ **Premedication** with dexamethasone:

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- Unless contraindicated, dexamethasone 4 mg is to be administered orally or IV twice daily for 3 days, beginning the day before administering Zynlonta® to mitigate pyrrolobenzodiazepine-related toxicities.
- If dexamethasone administration does not begin the day before Zynlonta®, oral or IV dexamethasone should begin at least 2 hours prior to administration of Zynlonta®.

Warnings and precautions [6]

- **Effusion and oedema**
  - Monitor for the development of pleural effusion, pericardial effusion, ascites, peripheral oedema, and general oedema.
  - Consider diagnostic imaging when symptoms develop or worsen.
- **Myelosuppression**
  - Monitor blood cell counts. Withhold, reduce, or discontinue Zynlonta™ based on severity.
- **Infections**
  - Monitor for infection and treat promptly.
- **Cutaneous reactions**
  - Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions.
  - Dermatologic consultation should be considered.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise patients of the potential risk to a foetus and to use effective contraception.

Study characteristics [7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
LOTIS-2, ADCT-402-201 NCT03589469	145	Loncastuximab tesirine administered on an outpatient basis IV over 30 min once every 3 weeks on day 1 of each 21-day cycle, at 150 µg/kg for the first two cycles followed by 75 µg/kg for subsequent cycles[2]	-	overall response rate assessed by central review	multicentre, open-label, single-arm, phase 2 trial	CD-19	ADC Therapeutics	[8]

Efficacy	Safety, primary analysis data
Primary analysis data (data cutoff 6 April, 2020) **Overall response rate (complete or partial response, in the as-treated population n=145):** 48.3% (39.9–56.7) **Complete response rate**: 24.1% (17.4–31.9)	**Patients with at least one treatment-emergent AE**: n=143/145 (99%) **Patients with at least one serious treatment-emergent AE**: n=57/145 (39%)

[2] For up to 1 year or until disease relapse or progression, unacceptable toxicity, death, major protocol deviation, pregnancy, or patient, investigator, or sponsor decision. Patients with clinical benefit could continue treatment beyond 1 year if agreed with the sponsor. Patients received oral dexamethasone premedication per protocol, unless contra-indicated, and were recommended to avoid prolonged exposure of skin to sunlight due to reports of light-sensitive skin rashes in the phase 1 study.

Complete response: 24% **Partial response**: 24% **Stable disease**: 15% **Progressive disease**: 21% **Not evaluable**: 16% **Median time to first response (complete response or partial response)**: 41.0 days (IQR 38.0–44.0) **Median duration of response**: 10.3 months (95% CI 6.9–NE) **Median duration of response for patients with a complete response**: 13.4 months (10.3–NE) **Median duration of response for patients with a partial response**: 5.7 months (1.7–NE) **Probability of responders maintaining responses for 9 months or longer**: 64% **Median PFS**: 4.9 months (95% CI 2.9–8.3) **Median OS**: 9.9 months (6.7–11.5) **Median relapse-free survival**: 13.4 months (10.3–NE) **Patients who received subsequent therapy after loncastuximab tesirine treatment**: 47%, including 6% of patients who had subsequent autologous HSCT (3%) or allogeneic HSCT (3%) as consolidation therapy. **Patients who received subsequent CD19-directed CAR T-cell therapy**: 10% **Investigator-assessed overall response rate to CAR T-cell therapy after loncastuximab tesirine**: 47%, of whom 40% had complete response	**Serious AEs that were considered at least possibly related to loncastuximab tesirine**: n=22/145 (15%) **Patients who died during the study period**: n=77/145 (53%) **Deaths due to disease progression:** n=60/77 (78%) **Patients who died from fatal treatment-emergent AEs**: n=5/77 (6%)[3] **Patients who died after the AE reporting period**: n=12/77 (16%)[4] **Treatment-emergent AEs leading to treatment discontinuation**: n=34/145 (23%) **Discontinuation of treatment during follow-up**: n=137/145 (94%); most commonly due to disease progression n=81/137 (59%)

HrQoL, symptoms and tolerability [10]

EQ VAS and FACT-Lym Scores

- Mean (standard deviation) EQ VAS score at baseline: 71.4 (19.1).
- The mean change from baseline in EQ VAS score showed a trend of improvement in the overall population in overall health over time.
- The mean change in EQ VAS score was above 0 starting from cycle 3, day 1, and reached the MID of 7 points at cycle 8. Although the sample size reduced considerably compared with baseline, the remaining patients after cycle 9 had even higher mean change from baseline score in EQ VAS.
- The adjusted improvement on EQ VAS overall health was 0.65 per cycle (95% CI, 0.26-1.04, p= 0.001). At cycle 9, day 1, the adjusted mean change from baseline score was 5.00, close to the MID (95% CI, 1.75-8.25, p= 0.003).
- Similarly, at each visit during treatment, a higher percentage of patients experienced meaningful improvement than they did deterioration.
- During treatment, all FACT-Lym WB and composite scores remained stable in overall patient population except for worsened social/family WB at some visits.
- Compared with baseline, there was no meaningful or statistically significant change in physical WB, TOI, and FACT-Lym total scores.
- The emotional WB and LymS scores were statistically improved, as shown in the small P values for cycle 2, day 1 and/or cycle 9, day 1, but the magnitude of the improvement was not meaningful.
- Social/family WB and functional WB declined slightly over time.
- The FACT-G total score (the sum of physical, social/family, emotional, and functional WB) generally remained stable.
- While there was no obvious difference in baseline scores between responders and non-responders, the improvement in EQ VAS was associated with clinical response.
- The mean change from baseline VAS score increased over time among responders. Among non-responders, it was maintained without deterioration.
- Most FACT-Lym WB and composite scores remained stable among responders and declined among non-responders.

Symptoms

- Of the symptoms assessed in the LymS of FACT-Lym, pain in certain parts of the body, being bothered by lumps/swelling, trouble sleeping at night, and fatigue ("get tired easily") were the most frequently reported at baseline (33%-59% reported "somewhat" to "very much").

[3]Sepsis, small intestinal perforation, septic shock, pneumonia, and acute kidney injury; all of which were considered unrelated or unlikely to be related to loncastuximab tesirine.

[4] Three patients had fatal AEs reported (DLBCL, haemoptysis, and disease progression), but cause of death was recorded as disease progression. Two patients had non-treatment-emergent AEs leading to death considered by the investigator as possibly related to loncastuximab tesirine: One patient with acute respiratory distress syndrome, which began 31 days after the last dose of study drug and was associated with suspected pulmonary infection; and one patient with interstitial lung disease, which began 63 days after the last dose of study drug and was associated with suspected disease progression.

- Most patients (≥80%) reported "not at all" or "a little bit" at baseline for being bothered by fever, night sweats, losing weight, itching, and loss of appetite.
- During the course of treatment, more patients reported improvement compared with baseline for pain, lumps/swelling, and losing weight for a majority of the visits (percentage of patients with improvement –percentage of patients with symptom worsening > 10 percentage points for a majority of the visits, and p< .05 or .10 for Wilcoxon signed rank test at several visits). Fever and night sweats did not change for most patients. Itching was the only symptom for which more patients experienced worsening with P value > .10 except one visit (p= .06 at cycle 7, day 1). For other symptoms (fatigue, trouble sleeping, and loss of appetite), there was no clear trend for improvement or worsening.

GP5-Based Patient-Reported Tolerability to Treatment

- When patients were asked how much they were bothered by the side effects of treatment at baseline, 81% reported "not at all" or "a little bit" and 5% reported "quite a bit" or "very much." This likely reflects residual side effects from previous treatments. Throughout all visits during treatment, most patents (> 60%) reported being "not at all" or "a little bit" bothered by side effects of treatment.

Elderly Patients

- More than half of the study population was elderly patients (aged ≥65 years).
- Results for HRQoL, symptoms, and tolerability were very similar to those for the overall population.
- Specifically, during treatment with loncastuximab tesirine, higher percentages of patients reported improvement for pain, lumps/swelling, and losing weight for the majority of visits. Itching was the only symptom for which more patients experienced worsening rather than improvement.
- The EQ VAS overall health score and most FACT-Lym scores were maintained or improved among elderly patients. The majority of elderly patients reported treatment tolerability.

ESMO-MCBS version 1.1 [11]

Disclaimer: Though not finally validated, but feasibility tested in [12], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, the original ESMO assessments were also carried out for haematological indications in new fact sheets and updates.

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR:48.3%, median DOR: 10.3 months	-	ORR ≥20-<40% AND DoR ≥9 months	3	+39% serious treatment-emergent AEs	QoL improved	-1/+1	3

Risk of bias - study level (case series) [13]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial	yes	yes	yes	yes
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	yes	yes	yes	unclear[5]	yes

Overall risk of bias: low

First published: 10/2022
Last updated: 07/2023

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DLBCL=diffuse large B-cell lymphoma, DNA=deoxyribonucleic acid, EMA=European Medicines Agency, EQ-VAS=EQ visual analog scale, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FACT-G=Functional Assessment of

[5] Currently, primary analysis data is available; the actual study completion date of LOTIS-2 was 08/2022 and final analysis data will be added as soon as available.

Cancer Therapy–General; FACT-Lym=Functional Assessment of Cancer Therapy–Lymphoma Subscale; FM=final magnitude of clinical benefit grade, HGBL=high-grade B-cell lymphoma, HR=hazard ratio, HRQoL=health-related quality of life, HSCT=haematopoietic stem cell transplantation, I=intervention, Int.=intention, MG=median gain, MID= minimally important difference; n=number of patients, NE=not estimable, NICE=National Institute for Health and Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TOI= Trial outcome index, VAS=visual analog scale, WB=well-being

References:

1. European Medicines Agency (EMA). Medicines. Zynlonta. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/zynlonta].
2. National Institute for Health Research (NIHR). Loncastuximab Tesirine for relapsed or refractory diffuse large B-cell lymphoma – third line. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/26558-Loncastuximab-Tesirine-for-Diffuse-Large-B-Cell-Lymphoma-V1.0-FEB2021.-non-CONF.pdf].
3. U.S. Food and Drug Administration (FDA). FDA grants accelerated approval to loncastuximab tesirine-lpyl for large B-cell lymphoma. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-loncastuximab-tesirine-lpyl-large-b-cell-lymphoma].
4. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: www.warenverzeichnis.apoverlag.at].
5. European Medicines Agency (EMA). Zynlonta: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/zynlonta-epar-product-information_en.pdf].
6. U.S. Food and Drug Administration (FDA). Zynlonta. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761196s000lbl.pdf].
7. Supplement to: Caimi PF, Ai W, Juan Alderuccio P, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2021.
8. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2021; 22: 790–800. [Available from: https://linkinghub.elsevier.com/retrieve/pii/S147020452100139X].
9. U.S. National Library of Medicine, ClinicalTrials.gov. Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (LOTIS-2) . [Available from: https://clinicaltrials.gov/ct2/show/NCT03589469].
10. Spira A, Zhou X, Chen L. Health-Related Quality of Life, Symptoms, and Tolerability of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Clinical Lymphoma, Myeloma and Leukemia, Vol 22, No 3, 158–168
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
12. Kiesewetter B., Cherny NI, Boissel N, et al. EHA evaluation of the ESMO—Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) for haematological malignancies. ESMO Open 2020;5:e000611.
13. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].